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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/941,450	08/28/2001	Casey C. Case	S7-US3 8325-0007.20	6791

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EXAMINER
BRUSCA, JOHN S

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 04/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/941,450	CASE ET AL.	
	Examiner	Art Unit	
	John S. Brusca	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *15,20-23 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,16-19,24 and 26-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3, 4, 6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of estradiol as the species of second molecule, expression of RNA as the species of phenotype, and human cells as the species of cell type in Paper No. 7 is acknowledged. The traversal is on the ground(s) that searching of all species does not represent a search burden. This is not found persuasive because each species is drawn to subject matter that is mutually exclusive and would each require a separate search. The applicants have provided no evidence that searching of one species would necessarily search all other species.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 15, 20-23, 25, and claim 17 in part are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7

Specification

3. The disclosure is objected to because of the following informalities: on page 51, line 20, an application is referred to by what appears to be a docket number rather than an application number.

Appropriate correction is required.

Information Disclosure Statement

4. In the information disclosure statement filed 27 February 2002 the reference Strausberg et al. was included but was not listed on the accompanying Form PTO 1449. The Strausberg et al. reference has been considered and is listed on the attached Form PTO 892.

5. In the information disclosure statement filed 27 February 2002 the reference "Goodman et al." does not appear as described in the corresponding publication of Nature. The corresponding publication International Human Genome Sequencing Consortium has been considered and is listed on the attached Form PTO 892.

Claim Rejections - 35 USC § 102

6. For the purpose of examination the claims have been considered to be anticipated or obvious over prior art that anticipates or makes obvious each step of the claimed methods. The preamble is not considered to affect the scope of the claimed subject matter.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 2, 4-12, 18, 19, and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Liu et al. (reference C1 in the information disclosure statement filed 24 February 2003).

The claims are drawn to a method of modulation of expression of a predetermined gene in a cell with a zinc finger protein and assaying the cell for a resulting change in phenotype. In some embodiments the gene expresses an mRNA and a protein. In some embodiments the zinc finger binds near the transcription start site or in a coding region of the gene. In some

embodiments the zinc finger protein comprises a VP16 activation domain or a KRAB repression domain. In some embodiments the cell is a human cell.

Liu et al. shows on pages 528-5529 and figure 4 modulation of expression of a target luciferase gene in a human cultured HeLa cell by introduction of an expression vector that expresses a zinc finger protein linked alternatively to a VP16 activation domain or a Krab-A repression domain. The phenotype measured was expression at the protein level of the luciferase gene product, which inherently also measures transcription of the luciferase gene. The zinc finger protein binds to a site in the promoter region of the luciferase gene (see page 5526). Liu et al. discusses use of zinc finger proteins to modulate gene expression by binding within the coding region in the first column of page 5529.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. in view of Heix et al.

The claims are drawn to a method of modulation of expression of a predetermined gene in a cell with a zinc finger protein and assaying the cell for a resulting change in ribosomal RNA.

Liu et al. shows on pages 528-5529 and figure 4 modulation of expression of a target luciferase gene in a human cultured HeLa cell by introduction of an expression vector that expresses a zinc finger protein linked alternatively to a VP16 activation domain or a Krab-A repression domain. The phenotype measured was expression at the protein level of the luciferase gene product, which inherently also measures transcription of the luciferase gene. The zinc finger protein binds to a site in the promoter region of the luciferase gene (see page 5526). Liu et al. discusses use of zinc finger proteins to modulate gene expression by binding within the coding region in the first column of page 5529. Liu et al does not show modulation of expression of a ribosomal RNA gene.

Heix et al. shows in the abstract and throughout that HeLa cell ribosomal RNA gene expression is regulated with the cell cycle. Heix et al. shows that cell transcription factor activity is modulated to effect the regulation of the ribosomal RNA genes during the cell cycle.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Liu et al. to target ribosomal RNA genes to further study the effects of the cell cycle on ribosomal RNA genes.

10. Claims 1, 13, 14, 16, 17, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. in view of Braselmann et al.

The claims are drawn to a method of modulation of expression of a predetermined gene in a cell with a zinc finger protein and assaying the cell for a resulting change in ribosomal RNA. In some embodiments the zinc finger is regulated by estradiol, and the cell is infected with a virus.

Liu et al. shows on pages 528-5529 and figure 4 modulation of expression of a target luciferase gene in a human cultured HeLa cell by introduction of an expression vector that expresses a zinc finger protein linked alternatively to a VP16 activation domain or a Krab-A repression domain. The phenotype measured was expression at the protein level of the luciferase gene product, which inherently also measures transcription of the luciferase gene. The zinc finger protein binds to a site in the promoter region of the luciferase gene (see page 5526). Liu et al. discusses use of zinc finger proteins to modulate gene expression by binding within the coding region in the first column of page 5529. Liu et al does not show regulation of a zinc finger protein by estradiol or infection of the cell with a virus.

Braselmann et al. shows in the abstract and throughout an estrogen regulated recombinant transcription factor which is fused to an estrogen regulated activation domain. Braselmann et al. shows that addition of estradiol activates expression of the targeted gene in figure 1. Braselmann et al. shows construction of a stable cell line Rat-1 Gal-ER that comprises the transcription factor gene by use of a viral expression vector on page 1658, allowing for additional selection for subsequent transfections with different vectors.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Liu et al. by use of the estradiol regulated activation domain of Braselmann et al. because Braselmann et al. shows that their system allows for inducible expression of cells by addition of estradiol at desired times. It would have been further obvious to use a viral infected cell because Braselmann et al. outlines a method of construction of cells comprising desired genes by use of viral vectors.

11. Claims 1, 26, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. in view of Hagmann et al.

The claims are drawn to a method of modulation of expression of a predetermined gene in a cell with a zinc finger protein and assaying the cell for a resulting phenotypic change. In some embodiments the gene is a viral gene.

Liu et al. shows on pages 528-5529 and figure 4 modulation of expression of a target luciferase gene in a human cultured HeLa cell by introduction of an expression vector that expresses a zinc finger protein linked alternatively to a VP16 activation domain or a Krab-A repression domain. The phenotype measured was expression at the protein level of the luciferase gene product, which inherently also measures transcription of the luciferase gene. The zinc

finger protein binds to a site in the promoter region of the luciferase gene (see page 5526). Liu et al. discusses use of zinc finger proteins to modulate gene expression by binding within the coding region in the first column of page 5529. Liu et al does not show regulation of a viral gene.

Hagmann et al. shows in the abstract and throughout that Herpes Simplex Virus (HSV) immediate early gene promoters are regulated by VP16 transcription factors. Hagmann et al. shows in figures 1-10 assays of activation of constructs in cells by VP16.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Liu et al. to study the HSV gene constructs of Hagmann et al. to further study the effect of VP16 on HSV gene expression because Liu et al. shows that their zinc finger proteins allow localization of VP16 to sequences of choice.

12. Claims 1 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. in view of Burge et al. (reference AF-1 in the Form PTO 1449 filed 23 January 2002).

The claims are drawn to a method of modulation of expression of a predetermined gene in a cell with a zinc finger protein and assaying the cell for a resulting phenotypic change. In some embodiments the predetermined gene is determined by a gene prediction algorithm.

Liu et al. shows on pages 528-5529 and figure 4 modulation of expression of a target luciferase gene in a human cultured HeLa cell by introduction of an expression vector that expresses a zinc finger protein linked alternatively to a VP16 activation domain or a Krab-A repression domain. The phenotype measured was expression at the protein level of the luciferase gene product, which inherently also measures transcription of the luciferase gene. The zinc finger protein binds to a site in the promoter region of the luciferase gene (see page 5526). Liu et al. discusses use of zinc finger proteins to modulate gene expression by binding within the

coding region in the first column of page 5529. Liu et al does not show use of target genes determined by a gene prediction algorithm.

Burge et al. shows in the abstract and throughout an algorithm for prediction of genes in genomic sequences.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Liu et al. by use of the gene prediction algorithm of Burge et al. for the purpose of applying the method of Liu et al. to study other genes of interest.

13. Claims 1 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. in view of Bailey et al. (reference AC-1 in the Form PTO 1449 filed 23 January 2002).

The claims are drawn to a method of modulation of expression of a predetermined gene in a cell with a zinc finger protein and assaying the cell for a resulting phenotypic change. In some embodiments the predetermined gene is determined by analysis of expressed sequence tags.

Liu et al. shows on pages 528-5529 and figure 4 modulation of expression of a target luciferase gene in a human cultured HeLa cell by introduction of an expression vector that expresses a zinc finger protein linked alternatively to a VP16 activation domain or a Krab-A repression domain. The phenotype measured was expression at the protein level of the luciferase gene product, which inherently also measures transcription of the luciferase gene. The zinc finger protein binds to a site in the promoter region of the luciferase gene (see page 5526). Liu et al. discusses use of zinc finger proteins to modulate gene expression by binding within the coding region in the first column of page 5529. Liu et al does not show determination of the target gene by analysis of expressed sequence tags.

Bailey et al. shows in the abstract and throughout a method of analysis of expressed sequence tags that allows for identification of corresponding genes in genomic sequences.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Liu et al. by use of the expressed sequence tag analysis method of Bailey et al. for the purpose of applying the method of Liu et al. to study other genes of interest.

14. Claims 1 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. in view of Gelfand et al. (reference AM-1 in the Form PTO 1449 filed 23 January 2002).

The claims are drawn to a method of modulation of expression of a predetermined gene in a cell with a zinc finger protein and assaying the cell for a resulting phenotypic change. In some embodiments the predetermined gene is determined by similarity to cDNA sequences.

Liu et al. shows on pages 528-5529 and figure 4 modulation of expression of a target luciferase gene in a human cultured HeLa cell by introduction of an expression vector that expresses a zinc finger protein linked alternatively to a VP16 activation domain or a Krab-A repression domain. The phenotype measured was expression at the protein level of the luciferase gene product, which inherently also measures transcription of the luciferase gene. The zinc finger protein binds to a site in the promoter region of the luciferase gene (see page 5526). Liu et al. discusses use of zinc finger proteins to modulate gene expression by binding within the coding region in the first column of page 5529. Liu et al does not show determination of the target gene by similarity to cDNA sequences.

Gelfand et al. shows in the abstract and throughout a method of analysis of cDNA sequences that allows for identification of corresponding genes in genomic sequences.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Liu et al. by use of the expressed sequence tag analysis method of Gelfand et al. for the purpose of applying the method of Liu et al. to study other genes of interest.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca whose telephone number is 703 308-4231. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on 703 308-4025. The fax phone numbers for the organization where this application or proceeding is assigned are 703 746-5137 for regular communications and 703 746-5137 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308-0196.

John S. Brusca
Primary Examiner
Art Unit 1631

jsb
April 5, 2003